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Research article

HRCT characteristics of severe emphysema patients: Interobserver variability among expert readers and comparison with quantitative software

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ABSTRACT

Purpose: For a successful bronchoscopic lung volume reduction coil treatment it is important to place the coils in the most emphysematous lobes. Therefore assessment of the lobe with greatest destruction is essential. Our aims were to investigate the level of agreement among expert reviewers of HRCT-scans in emphysema patients and the comparison with QCT (quantitative computed tomography) software.

Method: Five experienced CT-assessors, conducted a visual assessment of the baseline HRCT-scans of emphysema patients who participated in the RENEW bronchoscopic lung volume reduction coil study. On the same HRCT-scans, a QCT analysis was performed.

Results: In total 134 HRCT-scans were rated by all 5 experts. All 5 CT-assessors agreed on which was the most destructed lobe in 61 % of the left lungs (k:0.459) and 60 % of the right lungs (k:0.370). The consensus of the 5 assessors matched the QCT in the left lung for 77 % of the patients (k:0.425) and in the right lung for 82 % (k:0.524).

Conclusions: Our results show that the interobserver agreement between five expert CT-assessors was only fair to moderate when evaluating the most destructed lobe. CT-assessor consensus improved matching with QCT determination of lobar destruction compared to individual assessor determinations. Because some CT-features are associated with treatment outcomes and important for optimal patient selection of bronchoscopic lung volume reduction treatment, we recommend including more than one CT-reviewer and supported by QCT measurements.

1. Introduction

Computed tomography of the chest (CT scans) are important in patient selection for bronchoscopic lung volume reduction treatments, like the endobronchial valve or lung volume reduction coil treatment in Chronic Obstructive Pulmonary Disease (COPD) patients with emphysema [1,2]. CT features that are important include: interlobar fissure completeness, the degree and distribution of emphysematous destruction on a lobar level, and the presence of significant co-morbidity or abnormalities [2]. Quantitative assessment of CT-scans (QCT) by (semi-)

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automatic software is an important supportive tool. For bronchoscopic lung volume reduction with endobronchial valves, QCT is already incorporated in patient selection as it has proven additional value for the evaluation of fissure completeness [3,4].

Completeness of the target lobe fissure is not a prerequisite for bronchoscopic lung volume reduction treatment using coils. However, according to an expert panel recommendation, the coils should be placed in the lobe with the greatest degree of emphysematous destruction per lung in order to achieve optimal treatment outcome [5]. The RENEW-study, a large multicenter randomized controlled trial investigating the coil treatment, relied on a visual CT-analysis by the pulmonologist without support of QCT to select the most destructed lobes for treatment [6,7] A recent post-hoc analysis of the RENEW-study showed that 38 % of patients received one or both coil treatments in the ipsilateral lobe of lesser emphysematous destruction according to the QCT-analysis [7]. These patients had significantly inferior clinical outcomes one year after treatment compared to the patients who were treated in the most destructed lobes according to the QCT-analysis [7].

As emphysematous destruction and distribution are important for patient selection and treatment outcome of the coil treatment, we were interested in the level of interobserver agreement of visual CT analysis in these CT outcomes and whether QCT has additional value. Therefore, our aims were to investigate the level of agreement among expert reviewers of CT scans in patients with emphysema (and potential coil candidates) and the comparison between these expert reviewers and QCT software.

2. Material and methods

2.1. Study population and study design

We included patients in this analysis who were treated with coils in the intervention arm in the RENEW-study and completed the 12 month follow up period and had an evaluable baseline CT scan [6]. In the RENEW trial all the ethics committees of the participating hospitals approved the study and all patients provided informed consent. Four experienced pulmonologists (GC,FS,PS and DS) and one experienced chest radiologist (WM) involved in the RENEW-study conducted a visual assessment of the baseline CT scans. The CT-assessors only reviewed the baseline CT scans and were not informed about patient characteristics, treatment lobes or treatment outcome.

2.2. CT evaluation parameters and QCT-parameter

All patients underwent a full inspiration (TLC) and full expiration (RV) chest CT-scan according the standardized RENEW study scan protocol. Non-contrast scans were acquired at 120 kV, with effective tube current of 80–100 mA s depending on patient size. For lung evaluation, images were reconstructed at 1 mm, with kernel B40f.

The following characteristics on the CT were scored: the most destructed lobe (left upper versus left lower lobe and right upper versus right lower lobe (right middle lobe was not included because no coils are placed in this lobe)), emphysema severity of the target lobe (using a 0−3 Likert scale, 0 = no emphysema to 3= severe emphysema), heterogeneity score of the left and right lung (0= homogeneous to 3= very heterogeneous), presence of bronchial wall thickening, presence of bronchiectasis (both present versus not-present) and predicted clinical outcome (0= no response to 3= massive response). The QCT-analysis was performed using LungQ software (Thirona, Nijmegen, The Netherlands). The most destructed lobe according to the QCT-analysis was based on lobar percentage emphysema which was calculated as percentage of low attenuation areas below -950 Hounsfield units on inspiratory scans.

2.3. Other outcome parameters

Other outcome parameters which were measured at baseline and 1 year follow up were Residual Volume (RV) measured by body plethysmography, Forced Expiratory volume in 1 s (FEV_1) by spirometry (both according to the European Respiratory Society/ American Thoracic Society (ATS) guidelines [8,9]), 6-min walk distance(6MWD) measured by a 6MWD-test (according to the ATS guidelines [10]) and quality of life measured by the St. George's respiratory questionnaire (SGRQ total score) [11]. Furthermore, target lobe volume reduction (TLVR) was measured on the CT scan that was repeated 1 year after treatment.

2.4. Statistical analyses

Statistical analyses were performed with IBM SPSS statistics version 23 (IBM, Armonk, USA) or Minitab version 19 (Pennsylvania, USA). P-values below 0.05 were considered statistically significant. To establish the agreement for categorical variables between CT-assessors a Cohen's Kappa was calculated in case of 2 CT-assessors and a Fleiss Kappa in case of more than 2 CT-assessors. For continuous variables an intraclass correlation (ICC) coefficient was calculated. The level of agreement was interpreted as follows: poor $k<0$, slight $0<k<0.2$, fair $0.21<k<0.4$, moderate $0.41<k<0.6$, substantial $0.61<k<0.8$ and almost perfect $0.81<k<1.0$. [12] For the comparison between QCT and the five CT-assessors we used the consensus of the assessors, which was the lobe that was most frequently chosen as most destructed by the 5 assessors. Furthermore, a Pearson correlation coefficient was calculated to investigate whether there was an association between the predicted clinical outcome based on the CT-scan by the CT-assessors and the change after one year in the following clinical outcomes: FEV_1, RV, 6MWD, SGRQ and TLVR.

3. Results

Baseline CT-scans of 134 patients (47 %male, mean FEV_1: 26 %pred, RV 244 %pred, 6MWD:318 m, SGRQ: 59 units) were rated by all 5 experts (patient and CT characteristics can be found in Table 1 and a flowchart of patient selection in Fig. 1). Table 2 shows the agreement between the 5 CT-assessors in the different CT-scan characteristics. In 61 % of the patients all 5 CT-assessors agreed with the most destructed lobe of the left lung, in 20 % 4 CT-assessors were in agreement and in 19 % 3 CT-assessors were in agreement (Fleiss Kappa: 0.459). For the right lung this was 60 %, 24 % and 16 % respectively (Fleiss Kappa: 0.370). There was a moderate interobserver agreement between the 5 CT-assessors in left target lobe severity (ICC: 0.519) and right target lobe severity (ICC:0.561) and a fair agreement in left and right lung heterogeneity score (ICC: 0.394 and 0.414 respectively), presence of bronchiectasis (Fleiss Kappa: 0.254) and predicted clinical outcome (0.398). Furthermore, there was a poor agreement in the presence of bronchial wall thickening (Fleiss Kappa: −0.127). The consensus of the 5 assessors were in agreement with QCT about which was the most destructed lobe in the left lung for 77 % of the patients (Cohen's Kappa: 0.425) and for the right lung in 82 % of the patients (Cohen's Kappa: 0.524) (Tables 2 and 3). Fig. 2 shows 2 examples of one CT-image with no agreement between the 5 assessors and one with complete agreement. There was a significant association between the overall predicted clinical outcome at baseline and change in FEV_1 (r: 0.271, p:0.002) and change in RV (−0.275, p:0.001) and TLVR (−0.343, $p<0.001$) but not with change in 6MWD or SGRQ total score (Table 4).

4. Discussion

Accurate lung HRCT assessment is of great importance in patient evaluation for lung volume reduction techniques. Our results show that the interobserver agreement between five expert CT-assessors was only

Table 1
Patient characteristics (n = 134).

Gender, *male (%)*		63 (47 %)
Race	*White*	127 (95 %)
	Black or african american	6 (5 %)
	Other	1 (0.7 %)
Age, years		63 ± 8.0
FEV_1, *%predicted*		25.7 ± 6.3
RV, *%predicted*		244 ± 38
DLCO, *%predicted*		34.6 ± 10.6
6MWD, *meter*		318 ± 80
SGRQ, *total score*		59.4 ± 12.4
mMRC, *score*		2.87 ± 0.73
Treated lobes	*Upper lobes*	102 (76 %)
	Lower lobes	15 (11 %)
	1 upper en 1 lower lobe	14 (10 %
	Right upper lobe only	3 (2 %)
Consensus assessors most destructed lobe*		
Left lung	Upper lobe /Lower lobe	82 %/18 %
Right lung	Upper lobe /Lower lobe	85 %/15 %
Quantitative CT outcomes		
Left lung- most destructed lobe	Upper lobe /Lower lobe	65 %/35 %
Right lung- most destructed lobe	Upper lobe /Lower lobe	65 %/35 %
Left lung- heterogeneity (absolute)		10.7 % (0.13−56.7)
Right lung- heterogeneity (absolute)		10.4 % (0.06−61.6)

Data are presented as number (%), mean ± standard deviation or median (range).
FEV_1: Forced expiratory volume in 1 s, RV: residual volume, DLCO: diffusing capacity for carbon monoxide, 6MWD: 6-min walk distance, SGRQ: St. George's respiratory questionnaire, mMRC: modified medical research council dyspnea scale.
'Consensus assessors' was the lobe that was most frequented chosen as most destructed by the 5 assessors.

fair to moderate when evaluating the most destructed lobe, target lobe destruction severity, presence of bronchiectasis and heterogeneity within the lung and only poor for the presence of bronchial wall thickening. When combining the mean consensus of the CT-assessors with QCT, the number of patients of which there was an agreement on what was the most destructed lobe increased.

The interobserver agreement between CT-assessors about which is the most destructed lobe was only fair to moderate. All 5 reviewers agreed on the most destructed lobe in approximately 60 % of the patients and the highest agreement between 2 reviewers was 80 %, demonstrating a large interobserver variability. Our post-hoc efficacy analysis of the RENEW study showed that it is crucial to treat the most emphysematous destructed lobe [7]. The choice of the most destructed lobe will probably be more difficult in more homogeneous distributed emphysema. Which is in line with that the patients of which the CT-assessors did not agree on did have a more homogeneous distribution of the emphysema which could attribute to this (left lung: 16.4 % heterogeneity difference vs 8.6 % and right lung 16.6 % vs 8.8 %, both $p < 0.05$). However, also the interobserver agreement on the heterogeneity score of the lung between CT-assessors was fair.

Our results show that when combining the consensus of CT-review by experts with QCT that the agreement of which was the most destructed lung lobe increased (left lung 61 %–77 % and right lung 60 %–82 %). Suggesting the additional value of QCT and multiple CT-reviewers, especially for a treatment like the coil treatment when lobar target selection is important for treatment outcome. Especially when no clear target lobe can be identified, addition of QCT could be helpful. Of course, it is not feasible to review every CT by 5 individuals but probably 2 reviewers could already be useful to obtain a higher yield. The CT-assessors in this study were experts in the field of bronchoscopic lung volume reduction treatments, so probably the use of QCT would be even more important with less experienced CT-reviewers. The published protocol of the ELEVATE trial, a randomized controlled trial investigating the coil treatment [13], shows that the trial will include QCT for the selection of the most destructed lobe besides a panel of two respiratory physicians and two radiologist.

In the past, for the visual review of fissure completeness also fair to moderate agreements were found between highly experienced pulmonologists and radiologists [14]. QCT-software was developed which was found to be comparable to expert radiologist review [15]. Currently, QCT is part of the patient selection for the bronchoscopic lung volume reduction treatment using endobronchial valves. However, also for this purpose QCT is proposed as supportive tool on top of the visual review and not as standalone tool [15].

Besides the evaluation of the level of destruction and heterogeneity of destruction on CT scan, for the coil treatment it is also important to assess the type of emphysema, as severe panlobular emphysema, giant bullae and paraseptal emphysema are not suitable emphysema patterns for treatment [5]. And also the absence of airway disease as this was found to be a predictor of response [7]. We only scored the presence of bronchial wall thickening and found that the agreement was poor. The other visual CT features were not scored systematically in this analysis. However, Barr et al. did investigate the interobserver agreement between a large group of radiologists and pulmonologist of these visual CT features in COPD patients and controls [16]. They found a moderate agreement (k range: 0.41−0.6) for absence or presence of emphysema

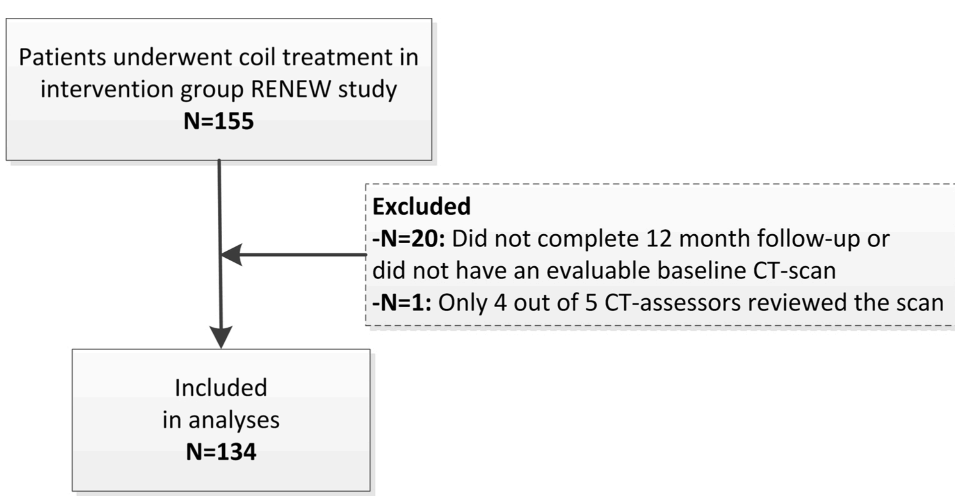

Fig. 1. Flowchart of patient selection.

Table 2
Agreement in CT-scan characteristics between the 5 assessors.

	n (%)	Agreement
Most destructed lobe		
Left lung		0.459*
All 5 assessors in agreement	66 (61 %)	
1 assessor in disagreement	22 (20 %)	
2 assessors in disagreement	21 (19 %)	
Consensus assessors vs QCT	101 (77 %)	0.425¶
Right lung		0.370*
All 5 assessors in agreement	64 (60 %)	
1 assessor in disagreement	26 (24 %)	
2 assessors in disagreement	17 (16 %)	
Consensus assessors vs QCT	106 (82 %)	0.524¶
Target lobe emphysema severity (0−3)		
Left target lobe		0.519$^{\Delta}$
Right target lobe		0.561$^{\Delta}$
Heterogeneity score (0−3)		
Left lung		0.394$^{\Delta}$
Right lung		0.414$^{\Delta}$
Presence of bronchial wall thickening?		
All 5 assessors in agreement-not present	3 (2 %)	−0.127*
According to 1 assessor present	74 (55 %)	
According to 2 assessors present	44 (33 %)	
According to 3 assessors present	12 (9 %)	
According to 4 assessors present	1 (1 %)	
All 5 assessors in agreement- present	0 (0 %)	
Presence of bronchiectasis?		
All 5 assessors in agreement-not present	93 (69 %)	0.254*
According to 1 assessor present	27 (20 %)	
According to 2 assessors present	7 (5 %)	
According to 3 assessors present	3 (2 %)	
According to 4 assessors present	3 (2 %)	
All 5 assessors in agreement- present	1 (1 %)	
Clinical outcome (0−3)		0.389$^{\Delta}$

Data are presented as number (%) and level of agreement measured by *=Fleiss kappa, ¶=Cohen's kappa or Δ=intraclass coefficient (ICC). Not all assessors assessed all CT-scan parameters, therefore the numbers differ.
Scoring: Target lobe emphysema severity (0−3): 0 = none, 1=mild, 2=moderate, 3=severe. Heterogeneity score 0−3; 0=homogeneous, 3=heterogeneous. Clinical outcome (0−3): 0= no response/don't treat, 1= mild response, 2= moderate response, 3= massive response.
'Consensus assessors' was the lobe that was most frequented chosen as most destructed by the 5 assessors. QCT = quantitative computed tomography analysis.

and presence of panlobular emphysema and a fair agreement (ĸ range: 0.21−0.4) for centrilobular emphysema, paraseptal emphysema, bulla and bronchial wall thickening [16]. As these are also fair to moderate agreements probably it would be helpful if visual CT-analysis could be combined with QCT for these features as well. Quantitative software is developed to quantify bronchial wall thickening [17] and also deep learning techniques to classify different emphysema patters [18], which both could be useful. Nambu et al., even concluded that in the assessment of the degree of airway disease in COPD, QCT might even be superior to visual assessment [19]. Furthermore, these CT-features are not only relevant for the coil treatment but for other bronchoscopic treatments as well.

The interobserver agreement between the CT-assessors in the prediction of clinical outcome was fair, which is not surprising as we believe it would be difficult to predict clinical response from the CT-scan alone. However, it was an interesting finding that the overall prediction was associated with an improvement in FEV_1, RV and decrease in target lobar volume on CT-scan and not with exercise capacity or quality of life. So, the prediction was more suitable for more physical outcomes directly related to the lung volume reduction effect and less for outcomes that are also influenced by other factors. Which is in line with another post-hoc analysis of the RENEW-study [20], were we found that for example the improvement in exercise capacity and quality of life also was affected by the presence of cardiac disease.

A strength of our analysis is that 5 expert CT-assessors who specifically have a lot of experience in assessing CT-scans of patients with severe emphysema and who are potential candidates for a lung volume reduction treatment were included. Furthermore, each CT-assessor assessed 134 CT scans, which is a large number for this kind of analysis. A limitation was the scoring of the presence of bronchial wall thickening and presence of bronchiectasis, which was only scored as present or not present. As the severity of both characteristics is much more clinically relevant than present or not present, changing this would have provided more useful information. Furthermore, it would have been useful if also the type of emphysema (like panlobular emphysema, presence of giant bullae and paraseptal emphysema) and the presence of airway disease were scored systematically, for example with use of the phenotypes defined by the Fleischner society [21].

In conclusion, we found a large variability between visual CT assessment among a group of expert CT-reviewers. Because some CT-features are associated with treatment outcomes and important for patient selection of bronchoscopic lung volume reduction treatment, we advise in case of doubt to include more than one CT-reviewer and to use QCT as a supportive tool, which both can be perfectly done in a multidisciplinary team setting [22]. Furthermore, the development of QCT software that could provide information on emphysema type and presence of airway diseases would be very useful.

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CRediT authorship contribution statement

Jorine E. Hartman: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing - original draft. **Gerard J. Criner:** Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. **William H. Moore:** Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. **Eva M. van Rikxoort:** Data curation, Formal analysis, Investigation, Methodology, Software, Writing - review &

Table 3
Agreement in most destructed lung lobe between 2 assessors or between 1 assessor and QCT.

	Rater 1		Rater 2		Rater 3		Rater 4		**Rater 5**	
	Left lung Agreement	*Right lung* Agreement	*Left lung* Agreement	*Right lung* Agreement	*Left lung* Agreement	*Right lung* Agreement	*Left lung* Agreement	*Right lung* Agreement	***Left lung*** Agreement	***Right lung*** Agreement
Rater 1			0.310 (69 %)	0.301 (70 %)	0.399 (73 %)	0.320 (70 %)	0.433 (75 %)	0.326 (73 %)	0.495 (77 %)	0.370 (73 %)
Rater 2					0.504 (87 %)	0.417 (85 %)	0.442 (84 %)	0.490 (89 %)	0.475 (85 %)	0.340 (83 %)
Rater 3							0.415 (82 %)	0.240 (80 %)	0.521 (86 %)	0.424 (83 %)
Rater 4									0.644 (89 %)	0.386 (85 %)
QCT	0.517 (77 %)	0.518 (78 %)	0.370 (75 %)	0.394 (77 %)	0.420 (76 %)	0.512 (81 %)	0.391 (75 %)	0.244 (72 %)	0.508 (80 %)	0.499 (80 %)

Data are presented as Cohen's kappa (percentage of scans that were in agreement).
QCT: quantitative computed tomography analyses.

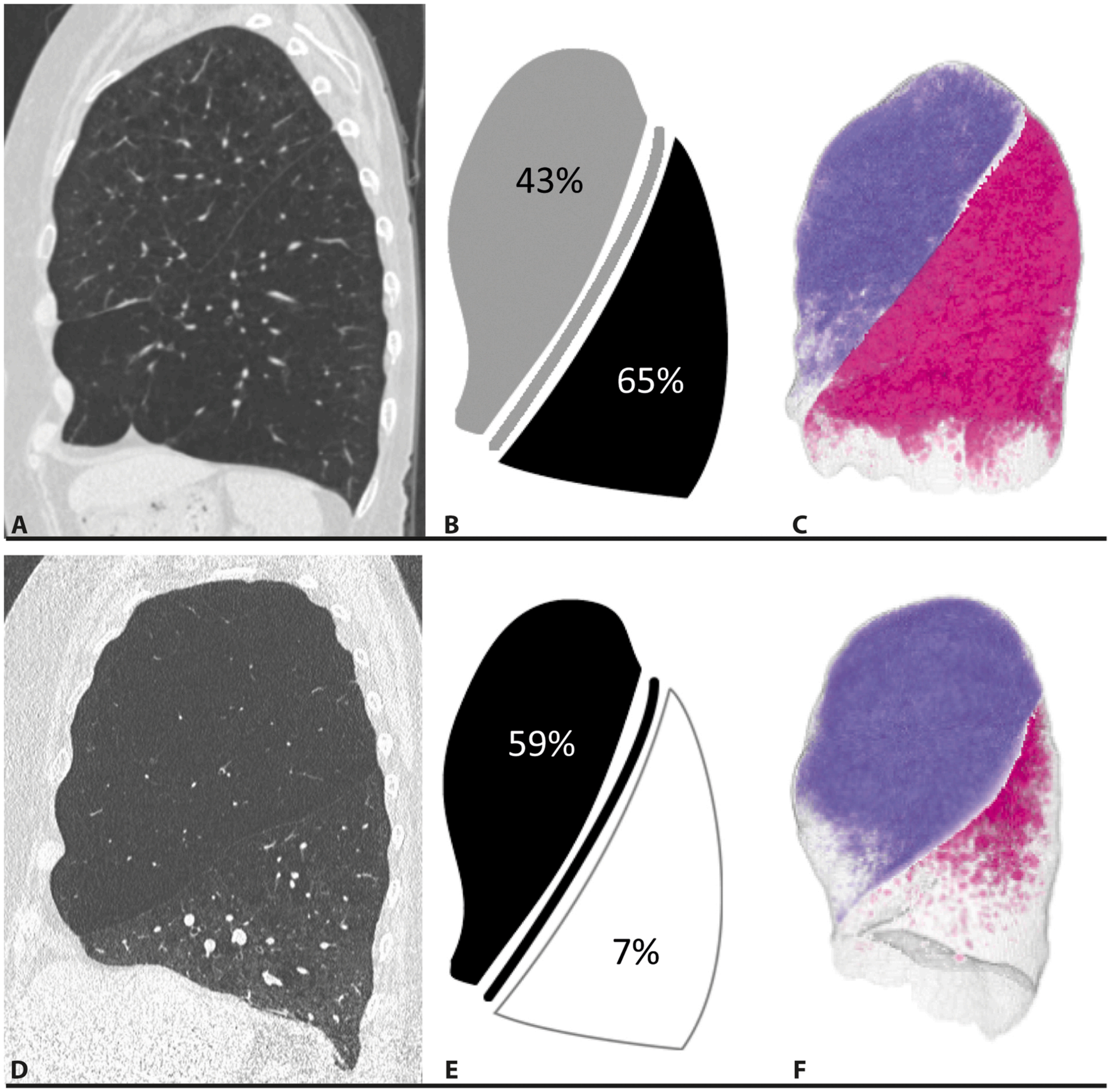

Fig. 2. Examples of an CT-image of which there was no or complete agreement of which was the most destructed lobe.
A&B&C) Example of CT-image and QCT analysis in which there was not complete agreement: 3 assessors identified the left lower lobe as most destructed and 2 the left upper lobe.
D&E&F) Example of CT-image and QCT analysis in which there was complete agreement: all 5 assessors identified the left upper lobe as most destructed.
Percentage shown in the right panels are the percentage of low attenuation areas below -950 Hounsfield units on inspiratory scans measured by quantitative CT analysis.

Table 4
Association between predicted clinical outcome based on baseline CT-scan and change in clinical outcomes 1 year after treatment.

	Δ FEV_1		Δ RV		Δ 6MWD		Δ SGRQtotalscore		TLVR	
	r	*p-value*	*r*	*p-value*	*r*	*p-value*	*r*	*p-value*	*r*	*p-value*
Rater 1	**0.246**	**0.004**	**−0.194**	**0.025**	0.161	0.063	−0.134	0.122	**−0.271**	**0.002**
Rater 2	**0.221**	**0.010**	**−0.316**	**<0.001**	0.016	0.856	−0.119	0.170	−0.104	0.244
Rater 3	0.024	0.786	−0.117	0.183	0.065	0.461	−0.016	0.857	**−0.184**	**0.042**
Rater 4	**0.178**	**0.042**	**−0.203**	**0.020**	0.068	0.436	−0.047	0.591	**−0.348**	**<0.001**
Rater 5	**0.271**	**0.002**	**−0.180**	**0.037**	0.125	0.150	−0.087	0.317	**−0.275**	**0.002**
Average opinion	**0.271**	**0.002**	**−0.275**	**0.001**	0.122	0.159	−0.105	0.227	**−0.343**	**<0.001**

Data are presented as r: Pearson's correlation coefficient and p-value. Values in bold were statistically significant ($p < 0.05$).
Δ= change between baseline and 1 year after coil treatment, FEV_1: forced expiratory volume in 1 s, RV: residual volume, 6MWD: 6-min walk distance, SGRQ: St. George's respiratory questionnaire, TLVR: target lobe volume reduction on expiratory CT scan.

editing. **Frank C. Sciurba:** Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. **Pallav L. Shah:** Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. **Rozemarijn Vliegenthart:** Investigation, Methodology, Validation, Visualization, Writing - review & editing. **Jorrit B.A. Welling:** Conceptualization, Investigation, Methodology, Writing - review & editing. **Dirk-Jan Slebos:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing.

Declaration of Competing Interest

EvR is co-founder, shareholder and managing director of Thirona, the company that developed and performed the quantitative CT-analysis. RV is supported by an institutional research grant from Siemens Healthineers. All other auteurs don't have any conflicts of interest related to this manuscript.

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